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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☐ *Additional inventors are being named on th____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

Methods and Articles for Remote Magnetically Induced Treatment of Cancer and Other Diseases, and Method for Operating Such Article

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Respectfully submitted,

SIGNATURE Glen E Books

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Methods and Articles for Remote Magnetically Induced Treatment of Cancer and Other Diseases, and Method for Operating Such Article

Inventors: Sungho Jin and Thomas Pisanic, MAE Dept., UCSD

Field of Invention

The present invention relates to a remote magnetic treatment of diseases and, in particular, to methods of treating diseased tissues, such as cancers or tumors, utilizing implantable magnetic articles and remotely applied magnetic fields.

Background of the Invention

Improved methods and articles for treating cancers and tumors are of extreme importance. According to the National Institute of Health, ~45% of males and 39% of females will be diagnosed with some form of cancer in his/her lifetime. The emotional and economic burden of cancer to the affected individual, family and the society is tremendous. It has been estimated that the US will lose $172 billion in the year 2002 due to cancer. See R. Etzioni, et al., *"The Case for Early Detection",* Nature Reviews: Cancer, Vol. 3, page 1-10, 2003. This cost arises from medical expenses, loss of work productivity due to illness, and the cost of premature death. Beyond economics, there is no dollar value that can be placed on the emotional trauma a person goes through after being diagnosed with cancer.

The survival rates of cancer patients have improved significantly in the last forty years, from 30% in the 1950s to 64% in the 1990s. See L. Ries, et al, *SEER Cancer Statistics Review, 1975-2000* , National Cancer Institute, Bethesda, MD, 2003. The

formula for the improvement in cancer survival rate has been the use of imaging technology for early detection, followed by surgical removal and possibly chemotherapy or radiotherapy. For patients who retain cancer cells in the body after surgery, the follow-up therapy, such as the chemotherapy drug delivery, is crucial for survival. Because of the severe toxicity often associated with cancer chemotherapy drugs, the practical usable dose for oral or injection administration is restricted, often to levels insufficient for cancer elimination. Targeted local delivery of cancer drugs is therefore important to enhance the therapeutic effect of chemotherapy. See "Controlled Drug Delivery" edited by K. Park, American Chemical Society, Washington DC, 1997.

It is desirable to further advance cancer treatment in an effort to improve the survival rate. Research advances in basic sciences and nanotechnology have produced a plethora of novel discoveries and treatment techniques that will be useful for engineering the next generation of cancer imaging systems. Information obtained from research findings in tissue processes (e.g., angiogenesis), cell dynamics (e.g., cell migration), and genetics can be utilized for isolating and identifying targeting molecules. Nanometer-sized materials have unique optical, electronic, and magnetic properties that can be tuned by changing the size, shape, or composition. These materials are useful for creating new cancer therapeutic techniques and precursors for building new cancer treatment therapeutic agents. For example, targeted drug delivery using polymer-base carriers can allow higher dose cancer drugs to the localized tumor regions with minimal adverse effects on the human body. Most of the conventional drug delivery techniques depend on natural, slow diffusion of drugs from the delivery carrier or capsule, without

active control in terms of delivery initiation time, duration, delivery profile, termination time, etc.

Summary of the Invention

This invention describes unique treatment methods and innovative articles that can be placed in a human or animal body to enable controlled destruction of diseased tissue and a totally externally controllable drug delivery process with a capability to start and stop the drug delivery at any time, for any duration. This invention deals with two aspects of diseased cell destruction, i.e., (A) magneto-mechanical disturbance of cell structure (e.g. cancer cells) for cell lysis and (B) magnetically activated drug release at local regions (e.g. tumors) from the magnetic-particle-containing drug reservoir. The invention also deals with combining both of the above mechanisms for dual therapy, as well as combining one or both of them with magnetic hyperthermia for multifunctional cell destruction therapy, and combining them with magnetic MRI for monitoring the accuracy of placement as well as for following up the cancer destruction progress and appropriate reprogramming of the magneto-mechanical therapy and remote-controlled chemotherapy drug release.

Brief Description of The Drawings

The nature, advantages and various additional features of the invention will appear more fully upon consideration of the illustrative embodiments now to be described in detail with the accompanying drawings. In the drawings:

Fig. 1 schematically illustrates various types of magnetic particle materials suitable for cancer treatment;

Fig. 2 represents TEM micrographs of exemplary magnetic nanoparticles suitable for cancer treatment, (a) spherical superparamagnetic Fe_3O_4 particles, (b) elongated ferrimagnetic gamma-Fe_2O_3 particles;

Figs. 3(a), (b) schematically illustrates before and after tumor cell damage caused by rotation of elongated magnetic particles;

Figs. 3(c),(d) schematically illustrate before and after tumor cell damage caused by oscillating lateral motion of magnetic nanoparticles;

Fig. 4. shows an apparatus for providing (a) rotational, and (b) oscillatory lateral magnetic field for particle movement;

Fig. 5. Magnetically-activated, targeted cancer drug release via (a) hyperthermia heating, (b) applied magnetic field, (c) magnetic-induced vibration, and (d) frictional wear.

It is to be understood that the drawings are for purposes of illustrating the concepts of the invention and are not to scale.

Detailed Description of the Invention

This invention provides several approaches to diseased cell destruction, i.e., (A) magneto-mechanical disturbance of cell structure for cell lysis and (B) magnetically activated drug release at local regions from a magnetic-particle-containing drug reservoir. The invention also includes combining both of the above mechanisms (A and B) for dual therapy, as well as combining one or both of the above mechanisms (A, B or A and B) with magnetic heating of disease cells to produce hyperthermia therapy for multifunctional cell destruction.

Nanoscale magnetic particles offer exciting possibilities for biomedical applications. These magnetic nanoparticles can easily be fabricated into small and controlled sizes comparable to or smaller than biological entities of interest, with their size ranging from ~2 – 100 nm as compared to proteins and genes (a few to tens of nanometers) and cells (a few to hundreds of microns). The unique advantages of magnetic nanoparticles for biomedicine applications include:

i). targeting by controlled binding or tagging to specific biomolecules or tumor cells, for example, by functionalizing with a coating of a polymer, dextran, silicon oxide or gold, and then conjugating with antibody or peptide. (see articles by M. Akeman, et al., "Nanocrystal targeting in vivo", PNAS, October 1, 2002, Vol. 99(20), p. 12617, and by

O. Mykhaylyk, et al., "Glial brain tumor targeting of magnetite nanoparticles in rats", Journal of Magnetism and Magnetic Materials, Vol. 225, p. 241-247, 2001.);

ii). mobility and navigability inside the animal or human body by externally guided magnetic fields;

iii) energy-transferable using applied ac magnetic field to perform localized tumor cell destruction via hyperthermia or help enhance chemotherapy with the raised temperature (see review articles by Q. A. Pankhurst et al., Journal of Physics D: Appl. Phys. Vol. 36, page R167–R181, 2003, and by P. Tartaj, et al., Journal of Physics D: Appl. Phys. Vol. 36, page R182–R197, 2003.),

iv). ability to offer contrast enhancement in magnetic resonance imaging (MRI). See the article by O. Mykhaylyk, et al. cited above.

These advantages are only beginning to be exploited for some limited biomedicine areas in recent years. In this invention, novel methods of targeted distribution of magnetic nanoparticles and unique operations to cause mechanical damage and destruction of cancer tumor cells are disclosed.

One cancer treatment technique that utilizes magnetic particles is magnetic hyperthermia. Hyperthermia is a therapeutic process using elevated tissue temperature for the treatment of diseased tissue such as cancer. Hyperthermia therapy consists of intentionally increasing tissue temperature to the range of ~41 to 45°C, for a period of 30 minutes to an hour, which advantageously damages tumor cells. Hyperthermia therapy kills cancer cells by various mechanisms such as protein denaturation,

impairment of membrane-related functions, inhibition of the synthesis and repair of damage to DNA, proteins, RNA, and heat damage of polysomes and microsomes.

While the biological and clinical effectiveness of hyperthermia has been proven, its utility has been restricted because of unacceptable coincidental heating of healthy tissues. The inability to localize hyperthermia to tumor regions has thus hindered the therapeutic application of hyperthermia. Magnetic particle hyperthermia provides a solution to this problem as it ensures preferential and localized heating of only the intended target tissue (e.g. tumors with targeted/bound magnetic nanoparticles). The therapeutic efficacy of targeted magnetic hyperthermia has been clearly demonstrated by a number of investigations, e.g., using magnetic liposomes and magnetic ferrofluids via animal experiments. See P. Moroz, et al., "Magnetically mediated hyperthermia:current status and future directions", *Int. J. Hyperthermia* 18, 267-284 (2002), M. Shinkai, et al., "Intracellular hyperthermia for cancer using magnetite cationic liposomes", *J. Magnetism and Magnetic Materials* 194 , 176-184 (1999), and A. Jordan, et al., "Presentation of a new magnetic field therapy system for the treatment of human solid tumors with magnetic fluid hyperthermia", *J. Magnetism and Magnetic Materials* 225, 118-126 (2001). In addition to the magnetic hyperthermia, magnetic nanoparticles have been utilized for cancer treatment via cell separation (such as for leukemia), or magnetic guidance of cancer drugs to the tumor sites.

In accordance with the invention, the effectiveness of such treatments can be significantly enhanced by introducing additional mechanisms of cancer cell destruction. The invention introduces two additional novel mechanisms of efficient cancer cell destruction. One method involves implanting rotatable or laterally oscillating magnetic

particles and applying a remote magnetic field to induce mechanical disturbance and lysis of cancer cells. The other is to implant cancer-drug-carrying magnetic particles which, on remote magnetic actuation, locally and specifically release cancer drugs to facilitate preferential damage of the cancer cells. Such a totally externally controllable drug delivery process offers a unique capability to start and stop the drug delivery at any time, for any durations, with any desired delivery profiles. Methods of applying such techniques are also disclosed.

In the design of magnetic nanoparticles and instrumentations for magnetic cancer treatment, it is important to understand the underlying physical behavior of magnetic nanoparticles, the movement of magnetic particles under different modes of applied magnetic field, and the mechanisms by which heat is generated in small magnetic particles by externally applied alternating current (AC) magnetic fields.

Magnetic particles move in the presence of a gradient magnetic field. Thus they can be made to rotate or oscillate with time-dependent changes in field direction and magnitude. In a uniform magnetic field, particle movement is less pronounced, however, particles tend to line up along the field direction, forming a chain-of-spheres configuration, thus altering the overall shape of particle-containing systems.

At a relatively high frequency AC magnetic field, the particles are heated, thus effectuating magnetic hyperthermia treatment. Enough heat must be generated by the particles to achieve and maintain tissue temperatures of at least ~41 °C for at least 30 minutes in order to kill the cancer cells. The mechanism of localized heat generation in

magnetic hyperthermia using non-superparamagnetic particles involves mainly the magnetic hysteresis loss of energy during a magnetization-demagnetization cycle.

Fig. 1 is a diagram schematically illustrating the magnetic hysteresis behavior of three types of magnetic particles relevant to the magnetic cancer treatment described in this invention. As the applied magnetic field (H) is increased from zero to a finite value and then reduced again in both positive and negative field directions, the material exhibits magnetization M-H loop, the characteristics of which depends on the type of magnetic material involved.

Hard magnetic materials have high coercivity (H_c) and remanent induction (M_r), and exhibit a large hysteresis loop behavior as illustrated in Fig. 1. The magnetically hard material is difficult to magnetize, requiring a strong applied field of e.g., 10 – 1000 KA/m (~120 – 12,000 gauss) to be fully magnetized. But once magnetized, it tends to retain magnet characteristics (high M_r) even after the applied field is removed (H=0). Soft magnetic materials are much easier to magnetize or demagnetize using a relatively weak magnetic field of ~10 – 100 KA/m (12 – 120 gauss), but the value of remanent induction is small. Superparamagnetic materials have extremely small particle sizes of typically ~10 nm or less in diameter (depending on the anisotropy of the material), exhibit no overall magnetic hysteresis and no remanent induction because of the magnetic moment fluctuation by thermal energy at a given temperature. An example of superparamagnetic Fe_3O_4 (magnetite) particles synthesized is shown in Fig. 2(a) as a transmission electron microscopy (TEM) picture. The magnetic susceptibility (the slope of the magnetization curve) and magnetic strength of superparamagnetic particles are significantly lower than those for the soft magnetic materials. Because of their zero or

small remnant induction, superparamagnetic particles and multi-domain soft magnetic particles usually do not agglomerate easily, which is desirable for magnetic hyperthermia or magnetic MRI applications. The hard magnetic particles tend to easily agglomerate due to their high remnant magnetization. Coated magnetic particles are less prone to agglomeration because of inter-particle gaps.

The magnetic hysteresis behavior of magnetic particles when exposed to a time-varying externally applied AC magnetic field produces magnetically induced heating. The amount of hysteresis-induced heat generated per unit volume is proportional to the frequency of the applied field multiplied by the area of the hysteresis loop in Fig. 1. Magnetically hard material with high coercive force, high remnance and large hysteresis loss can generate more heat. However, magnetically soft materials may have an operational advantage because of the ease of reaching a high magnetization state with a relatively low, practically available AC field. Also, the tendency of undesirable particle agglomeration with high coercivity materials can cause a problem in dispersion and targeted distribution of magnetic nanoparticles to the desired site. Superparamagnetic particles are ideal in this sense as there is no remanent magnetism in the absence of field to cause magnetic agglomeration.

From a practical point of view, the frequency and strength of the externally applied AC magnetic field that can be employed to generate the appropriate level of heating in a human is limited by deleterious physiological responses to high frequency magnetic fields such as undesirable stimulation of peripheral and skeletal muscles, possible cardiac stimulation and arrhythmia, and non-specific inductive heating of tissue. [See articles by J. R. Oleson, et al., "Hyperthermia by magnetic induction:

experimental and theoretical results for coaxial coil pairs", *Radiat. Res.* **95**, 175–186 (1983), and by J. P. Reilly, et al., "Principles of nerve and heart excitation by time-varying magnetic fields", *Ann. New York Acad. Sci.* **649**, 96–117 (1992).] A safe range of frequency and amplitude of AC field is considered to be approximately ~ 0.05–1.2MHz in frequency and ~0–15 kA/m in field strength (equivalent to ~0 - 180 gauss). The frequency and magnitude of the required field for efficient magnetic hyperthermia heating depends on several factors, such as the amount of magnetic nanoparticle material introduced, the nature and size of the magnetic material used, whether the nanoparticles are directly injected to the local tumor region, and the efficiency of tumor-targeted binding. A rough estimate is that several milligrams of magnetic material concentrated in each cubic centimeter of tumor tissue is appropriate for magnetic hyperthermia in human patients.[See the article by Q. A. Pankhurst, et al., cited earlier.]

Candidate magnetic nanoparticle materials suitable for the invention articles can be selected from ferromagnetic or ferrimagnetic materials with: i) generally larger multi-domain particles; ii) single-domain size particles (~8 – 30 nm size); or iii) smaller, superparamagnetic particles (~2-15 nm size). These particle sizes are considered sufficiently small to allow effective delivery to the site of the cancer, either via encapsulation in a larger moiety or suspension in some sort of carrier fluid. Nanoscale particles can be coupled with antibodies to facilitate targeting on an individual cell basis. The mechanism of heat generation associated with each type of materials can be different, offering unique advantages and disadvantages. The iron oxides magnetite (Fe_3O_4) and maghemite (γ -Fe_2O_3) are the most commonly used materials due to biocompatibility and suitable magnetic properties. Other highly magnetic nanoparticles

such as iron, nickel, cobalt, and magnetically soft ferrites such as Co-ferrite, Mn-Zn ferrite and Ni-Zn ferrite may also being considered.

For in vivo applications the magnetic particles must be coated with a biocompatible polymer such as various polymers, dextran, SiO_2, or gold, during or after the synthesis process to prevent the formation of large aggregates. The polymer or SiO_2 coating also enables relatively easy binding of therapeutic drugs to the magnetic particles via covalent attachment, adsorption or entrapment. See B. Denizot, et al., "Phosphorylcholine Coating of Iron Oxide Nanoparticles", *J. Colloid Interface Sci.* 209 66 (1999), and a book by U. Hafeli et al., *Scientific and Clinical Applications of Magnetic Carriers,* New York: Plenum, 1997.]. The main advantages of using nanoparticle sizes of less than 100 nm are their higher effective surface areas for easier attachment of ligands, lower sedimentation rates (high dispersion stability) and improved diffusion in tissues.

The magnetic nanoparticles for magneto-mechanical cell destruction or remote magnetic actuation for time-controllable drug delivery can be placed into the tumor by one or more of the following four mechanisms: 1). By injecting the magnetic nanoparticles into the blood vessel and allowing the tumor cell targeting to take place (e.g., by attached peptide or antibody on the particle surface); 2). By allowing the cells to naturally engulf (endocytosis) the particles, 3) By magnetically navigating/guiding the particles, e.g., dragging them using external permanent magnetic, or 4) By using magnetofection to force the particles to pass through the cell walls into intracellular regions, for example using a gradient magnetic field. For accuracy of targeted cancer cell destruction or drug delivery, the positioning of magnetic nanoparticles at or near the

tumor location and their distribution is desirably confirmed before the magneto-mechanical cell destruction is applied according to the invention. Either optical or MRI imaging can be utilized for this purpose.

(A). Tumor cell destruction using magneto-mechanical agitation

This approach uses magnetic nanoparticles coated with a biocompatible material such as dextran or silica, and then functionalized with peptide or antibody on the magnetic nanoparticle surface. The peptide or antibody on the magnetic particles allows targeting of the particles onto cancer cell surfaces. Alternatively, the particles can be moved toward and placed inside of the cancer cells by endocytosis of the cells themselves or by an intentional application of gradient magnetic field (e.g., ~100 – 10,000 Gauss/cm gradient) which can force the magnetic nanoparticles to move along the gradient direction passing through the cells on their way, and create an opportunity to get inside the tumor cells. Referring to Fig. 3(a)-(d), the magnetic nanoparticles 30 on or inside the tumor cells 31 are then made to move in a controlled manner and induce a magneto-mechanical disturbance of tumor cells, thus providing a novel cancer treatment. By utilizing elongated magnetic nanoparticles, such as maghemite (γ -Fe_2O_3) shown in Fig. 2(b), and applying a rotational magnetic fields such as by sequential actuation of remote electromagnets (40 of Fig. 4(a)), the particles can be made to rotate at appropriate frequencies. Such a nano-blender type mechanical motion can disrupt the cell structure regions 32 in the tumor, as illustrated in Fig. 3(b). An alternative way of producing cell damage by magneto-mechanical approach is to use a laterally oscillating gradient magnetic field (41 of Fig. 4(b)) to cause cell damage 32 as illustrated in Fig. 3(d).

Another embodiment of the inventive cancer treatment article and method is a combination of magneto-mechanical cell destruction and magnetic hyperthermia treatment. This approach is convenient as the same article (magnetic nanoparticles targeted and attached to the cancer cells) can be utilized for both mechanical movement and heating. This combination further enhances the overall probability of complete cancer elimination. Incomplete cancer cell destruction is often not an acceptable solution in cancer treatment because of cancer recurrence when even a small number of cancer cells remain.

A proper magnetic field magnitude, frequency, and field direction can in principle be formulated to achieve the goals of both magneto-mechanical cell destruction and magnetic hyperthermia simultaneously using the same magnetic treatment. However, a preferred treatment desirably consists of two steps, for example, a step of applying a rotating or laterally oscillating field within a somewhat lower frequency range of e.g., 1 Hz – 500 KHz for the magneto-mechanical cell destruction, and then a second step of applying a stationary, higher frequency field (e.g., 1KHz – 5 MHz) for magnetic hyperthermia. The two steps can be applied in series or they can be intermixed, as for example, alternately applying 10 minutes of each step.

The instrumentation suitable for magnetic hyperthermia therapy consists of a high frequency AC solenoid with adjustable frequency and amplitude in the range of ~ 0.1 KHz - 50 MHz (preferably 1KHz – 5 MHz) in frequency and ~0 – 1500 KA/m (0 - 180 gauss) , preferably 1 - 15 KA/m (12 - 180 gauss) in field strength. The use of a soft magnetic, high saturation, high-permeability core such as iron, Co-Fe, permalloy (Ni-Fe alloy), Ni-Zn ferrite or Mn-Zn ferrite is preferred for field amplifying purposes. The tissue

temperature rise during the AC field magnetic hyperthermia can be accurately measured using a non-metallic, optical fiber thermometer.

(B). Magnetic Drug Delivery

Therapeutic drugs for critical applications such as chemotherapies on tumors are typically administered in a non specific way. This is one of the main disadvantages of the current processes as the cytotoxic drug causes deleterious side-effects as it indiscriminately attacks normal, healthy cells as well. If the drug treatments could be localized, e.g. to the specific tumor site, very potent doses of effective agents could be utilized with minimal side effects.

In magnetically targeted drug therapy, according to the invention, a cytotoxic drug is either attached onto the surface of functionalized and properly conjugated biocompatible magnetic nanoparticle carrier, included inside a porous polymer containing magnetic particles in the pores, or encapsulated in magnetic liposomes. Some of these inventive drug/carrier complexes, such as biocompatible ferrofluids, can be injected into the patient's circulatory system, and the particles can either self-target toward the tumor cells due to the antibody conjugation added on their surface, or can be guided and kept in place by using external, high-gradient magnetic fields. Alternatively, they can be needle-injected into the tumor area followed by self-targeting, endocytosis or magnetofection. Once the drug/carrier is concentrated at the targeted organ, the drug can be released by a number of approaches such as via enzymatic activity, changes in physiological conditions such as pH, osmolality, or local temperature. Targeted drug delivery using these principles have been widely used for non-magnetic

drug delivery approaches. See the book on drug delivery by. K. Park cited earlier. Not much work has been done regarding the use of magnetic field for controlled drug release, although magnetic guidance to bring a drug toward an intended organ has been demonstrated. See C. Alexiou, et al., "Locoregional cancer treatment with magnetic drug targeting", *Cancer Res.* 60, 6641–8 (2000).

Generally, the magnetic particles in this invention are coated by a biocompatible polymer such as PVA or dextran, or inorganic coatings such as silica or gold. The coating protects the magnetic particle from the surrounding environment and also allows easier functionalization by attaching carboxyl groups, biotin, avidin, carbodi-imide and other molecules These functional group molecules then act as attachment points for the coupling of cytotoxic drugs or target antibodies to the carrier complex.

Some success in targeted delivery of magnetic drug carriers has recently been reported with human and animal experiments. A total remission of sarcomas was achieved in rats using magnetically targeted cytotoxic drugs, doxorubicin, implanted in rat tails. See K. J. Widder, et al., "Selective targeting of magnetic albumin microspheres containing low-dose doxorubicin - total remission in Yoshida sarcoma-bearing rats", *Eur. J. Cancer Clin. Oncol.* 19 135–139 (1983). A similar technique has been employed to target cytotoxic drugs to brain tumors. It was demonstrated that 10–20 nm magnetic particles were effective at targeting these tumours in rats with electron microscopy analysis showing that magnetic carriers were actually present in the interstitial space in tumors. See S. K. Pulfer, et al., "Distribution of small magnetic particles in brain tumor-bearing rats", *J. Neuro-Oncol.* 41, 99–105 (1999). Promising results related to magnetic targeting in humans were also reported. A Phase I clinical trial reported by Lubbe et al.,

"Physiological aspects in magnetic drug-targeting", *J. Magnetism and Magnetic Materials* 194, 149-155 (1999), demonstrated that drug-targeting with a ferrofluid (1% of the blood volume, Fe_3O_4 magnetic particle size of 100 nm, coated with a starch deravative) with the magnetic particles bound to "epirubicin" cancer drug, caused complete remissions of human colon as well as renal cancer. The reversible heteropolar binding of the drug epirubicin from the magnetic particles allowed the diffusion through the vessel wall into the tumor interstitial space. In addition, the article reported that the ferrofluid was successfully directed to the advanced sarcomas tumors without associated organ toxicity.

It is noted that these prior art techniques primarily deal with magnetic navigation and magnetic hyperthermia treatment, i.e., magnetic-field-assisted guiding of nanoparticle drug carriers and holding them in place for drug delivery, rather than magnetically actuated drug release.

Magnetically actuated drug release, according to the invention, offers many advantages, by virtue of the potential for programmable, remotely controlled drug release. This invention discloses such techniques with unique advantages such as being able to administer the drug therapy --- i) at any time, ii) for any duration, iii) at any programmable dose strength and release profile, iv) any-time termination of drug release. The techniques can be utilized for delivery of other drugs to human or animal organs for cure or alleviation of other non-cancer diseases or pains. Some example techniques of the inventive approaches to the "Magnetically Actuated Drug Release" are schematically illustrated in Fig. 5, and are described below.

i). Heating of a capsule 50 containing cancer drug(s) 51 via magnetic hyperthermia --- It is well known that there are many temperature sensitive polymers and hydrogels that can melt, swell or shrink to release drugs. See *Biorelated Polymers and Gels – Controlled Release and Applications in Biomedical Engineering*, T. Okano edited, Academic Press, Boston 1998, p. 93. For example, poly(N-isoporpylacrylamide)(NIPAAm) is one of the representative temperature-sensitive polymers with a lower critical solution temperature (LCST) of ~32°C. Such capsules are made to contain cancer drugs 51 and magnetic nanoparticles 52 together (or side by side in two adjacent chambers in a capsule), for example, using emulsion techniques. The drug can be dissolved in an aqueous solution or biocompatible solvent, in the form of deformable jelly, or in the form of nanoparticles mixed in the solidified polymer. The drug-containing nano-capsules, e.g., 20 – 2000 nm size, having a spherical, pancake or elongated rod shape, are then placed inside a human or animal body, either through injection into the blood stream, the tumor or the tumor region. The magnetic particles containing the desired cancer drugs are then placed inside the tumor by either injecting them into the blood vessel and allowing the tumor cell targeting to take place (e.g., by attached peptide or antibody on the particle surface), by letting the cells naturally engulf (endocytosis) the particles, by magnetically navigating/guiding the particles, e.g., dragging them using externally sweeping permanent magnets, or by using magnetofection forcing the particles to pass through the cell walls into intracellular regions, for example using a gradient magnetic field. For accuracy of targeted drug delivery, the positioning and distribution of the magnetic nanoparticles at or near the tumor location is desirably confirmed, e.g., by MRI imaging, prior to delivery of the drug.

Then an external magnetic field is applied so that the magnetic particles are locally heated, which in turn heats the temperature-sensitive polymer as well as the solution (such as saline, simulated body fluid solution, or other organic or inorganic solvent if the drug is already dissolved in the solution) in the polymer nanocapsule. The heating and expansion of the solution can cause the solution to leach out. Alternatively, the contraction of the polymer capsule diameter can cause the drug to leach out. These mechanisms are schematically illustrated in Fig. 5(a).

ii). Magnetic alignment and puncturing of capsule wall --- When a DC or AC magnetic field is applied (or removed), magnetic particles inside a drug-containing capsule move and rearrange themselves to reduce the overall magnetostatic energy. Either a formation of long chain-of-spheres or agglomeration and squeezing action of magnetic particles occurs depending on the initial state of particle arrangement, magnetic properties of the particles, and viscosity of the drug-containing matrix. The chain formation elongates the length, and could apply enough stress to squeeze out the liquid drug the from polymer pores, or puncture the capsule wall to release the drug, as illustrated schematically in Fig. 5(b).

iii). A high frequency AC field can induce magneto-mechanical vibration, which can aid the release of drug in a nanocomposite particle mix or slurry of magnetic nanoparticles, liquid-, jelly-, or particle-shaped polymer material, wherein the cancer drug is in the form of either a drug solution, drug jelly or drug nanoparticles, as illustrated schematically in Fig. 5(c).

iv). Elongated drug-carrying magnetic particles (or capsules) 53 can encounter significant frictional force on its ends if a high-speed rotating or oscillating magnetic field is applied. When the tip of the elongated particles (or capsules) containing the drug breaks off or wears away, the drug can be released from the ends, as illustrated schematically in Fig. 5(d).

The inventive magnetic nanoparticle cancer therapy can also be combined with magnetic-particle MRI (magnetic resonance imaging). The magneto-mechanical cell destruction treatment, the magnetic hyperthermia treatment, or the combination therapy of both can be combined with the magnetic-particle MRI for imaging and confirmation of the accuracy of magnetic therapy particles placement.

The principle of MRI relies on the counterbalance between the extremely small magnetic moment on a proton, and the very large number of protons present in biological tissue, allowing a measurable effect in the presence of high magnetic Fields. See articles by M. Browne and R. C. Semelka, *MRI: Basic principles and applications*, Wiley, New York 1999, and by J. D. Livingston, *Driving Force: The Natural Magic of Magnets*, Harvard Univ. Press, Cambridge, MA 1996.

The presence of very fine superparamagnetic or magnetic particles can enhance the contrast in MRI. Such a magnetic MRI imaging offers the advantage of high spatial resolution displaying contrast differences between tissues. In search of an effective contrast agents that will enhance and widen its diagnostic utility, there has been increasing interest and clinical diagnosis applications of contrast agents like dextran magnetite for MRI. See M. Shinkai, "Functional magnetic particles for medical

application", *J. of Biosci. and Bioeng.* 94(6), 606-613 (2002). Compared with paramagnetic ions, superparamagnetic iron oxide particles have higher molar relaxivities, and, when used as blood pool and tissue-specific agents, may offer advantages at low concentrations. Tumor-targeted magnetic MRI studies have also been conducted, demonstrating significant enhancement of MRI image contrast. See the article by O. Mykhaylyk, et al. cited earlier, an article by D. K. Kim, et al., "Characterization and MRI study of surfactant-coated superparamagnetic nanoparticles administeredinto the rat brain", *J. Magnetism and Magnetic Materials* 225, 256-261 (2001), and an article by C. Alexiou, et al., "Magnetic mitoxantrone nanoparticle detectionby histology, X-ray and MRI after magnetic tumor targeting", *J. Magnetism and Magnetic Materials* **225**, 187-193 (2001).

The present invention is also applicable for various types of medical treatments not related to the cancer treatment. For example, the unique advantages of the inventive magnetic remote drug delivery system, i.e. the capability to remotely administer the drug therapy from outside the body --- i) at any time, ii) for any duration, iii) at any programmable dose strength and release profile, iv) any-time termination of drug release, can be utilized for delivery of other drugs to human or animal organs for curing or alleviating of various diseases or symptoms, for example, delivery and controlled release of diabetes medications (insulin), gastrointestinal drugs, cardiovascular medicines, control drugs for brain functions and abnormal behavior, muscle control medicines, pain killers, antibiotics, gene therapy. The presence of magnetic particles can also be utilized to locally raise the temperature of the released drugs, via a

magnetic hyperthermia process, to accelerate the therapeutic efficiency of drug-cell interactions.

It is understood that the above-described embodiments are illustrative of only a few of the many possible specific embodiments which can represent applications of the invention. Numerous and varied other arrangements can be made by those skilled in the art without departing from the spirit and scope of the invention.

What is claimed is:

1. Article for treating diseased tissues comprising magnetic nanoparticles capable of destroying cells on external excitation of magneto-mechanical movement, using either rotational disturbance of elongated magnetic nanoparticles or lateral oscillatory movement of magnetic nanoparticles.

2. The article claim 1, in which the said particles are coated with a biocompatible material such as various polymers, dextran, silica or gold, and funtionalized and conjugated with cancer-cell-seeking targeting molecules such as an antibody or a peptide.

3. Method of treatment comprising implanting magnetic nanoparticles within a human or animal body and applying high frequency magnetic field using a device capable of applying sequential, rotating magnetic field to make the implanted magnetic nanoparticles rotate.

4. Method of treatment comprising implanting magnetic nanoparticles with a human or animal body and applying high frequency magnetic field using a device capable of applying laterally oscillating gradient magnetic field to induce implanted magnetic nanoparticles to move back and forth in a lateral direction.

5. The method of treatment comprising a combination of claims 3 and 4.

6. Method of targeting and placing magnetic nanoparticles within a human or animal body for externally controlled magneto-mechanical cell destruction therapy accomplished 1). by injecting tumor cell targeting magnetic nanoparticles into the blood vessel and allowing the tumor cell targeting to take place (e.g., by attached peptide or antibody on the particle surface), 2). by letting the cells to naturally engulf (endocytosis) the particles, 3) by magnetically navigating/guiding the particles, e.g., dragging them using external permanent magnetic, or 4) by using magnetofection forcing the particles to pass through the cell walls into intracellular regions, for example using a gradient magnetic field.

7. Combination therapy of the magneto-mechanical cell destruction of claim 1 together with magnetic hyperthermia therapy of raised cell temperature utilizing the same magnetic nanoparticles implanted and used for magneto-mechanical cell destruction.

8. Combination therapy of the magneto-mechanical cell destruction of claim 1 together with magnetic hyperthermia therapy, and magnetic MRI imaging for detection of the accuracy of placement of particles for magneto-mechanical cell destruction, and

progress monitoring of cancer cell destruction on repeated magneto-mechanical cell destruction therapy.

9. Magnetic nanoparticle/polymer/cancer drug nanocomposite system capable of remotely releasing cancer drugs on externally and remotely applied magnetic field and destructing cancer cells.

10. The method of the claim 9 wherein the cancer drug release is actuated by heating of the drug-containing and magnetic-particle-containing polymer, or the drug-attached and magnetic-particle-attached polymer via high frequency magnetic field applied.

11. The method of claim 10, wherein the cancer cell destruction by magnetically actuated drug release is also aided by magnetic hyperthermia based cancer cell destruction.

12. The method of claim 10, wherein the cancer cell destruction by magnetically actuated drug release is also aided by enhanced drug-cell interaction by the temperature rise of the drug on high frequency magnetic field applied.

13. The method of the claim 9 wherein the cancer drug release is actuated by magnetic particle re-alignment and puncturing of the implanted and targeted capsule wall of the drug-containing and magnetic-particle-containing polymer upon application of external magnetic field.

14. The method of the claim 9 wherein the cancer drug release is externally actuated by magneto-mechanical vibration of cancer-drug-containing nanocomposite system comprising particle mix or slurry of magnetic nanoparticles, liquid-, jelly-, or particle-shaped polymer material, and the cancer drug being in the form of either drug solution, drug jelly or drug nanoparticles.

15. The method of the claim 9 wherein the cancer drug release is externally actuated by a frictional force on its ends caused by a high-speed rotating or oscillating magnetic field applied, with the tip or edge of the drug-containing-elongated-particles (or capsules) breaking off or wearing away and releasing the drug.

16. The remote magnetically controllable drug release applied for non-cancer therapeutic treatments for human or animal, such as release of insulin for diabetes, gastrointestinal drugs, cardiovascular medicines, control drugs for brain functions and abnormal behavior, muscle control medicines, pain killers, or antibiotics utilizing the articles, apparatus and methods described in any of the claims 9 – 15.

ABSTRACT

This invention describes unique treatment methods and innovative articles that can be placed in human or animal body to enable controlled destruction of diseased tissue and a totally externally controllable drug delivery process with a capability to start and stop the drug delivery at any time, for any duration. This invention deals with two aspects of diseased cell destruction, i.e., (A) magneto-mechanical disturbance of cell structure (e.g. cancer cells) for cell lysis and (B) magnetically activated drug release at local regions (e.g. tumors) from the magnetic-particle-containing drug reservoir. The invention also deals with combining both of the above mechanisms for dual therapy, as well as combining one or both of them with magnetic hyperthermia for multifunctional cell destruction therapy, and combining them with magnetic MRI for monitoring the accuracy of placement as well as for following up the cancer destruction progress and appropriate reprogramming of the magneto-mechanical therapy and remote-controlled chemotherapy drug release.

Drawings

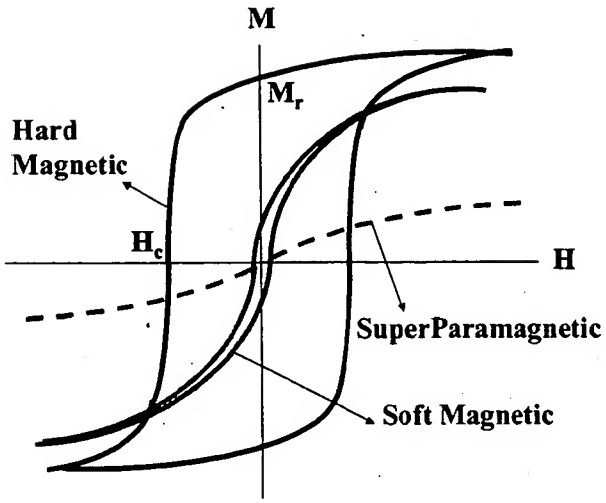

Fig. 1. Magnetization loops for various types of magnetic materials.

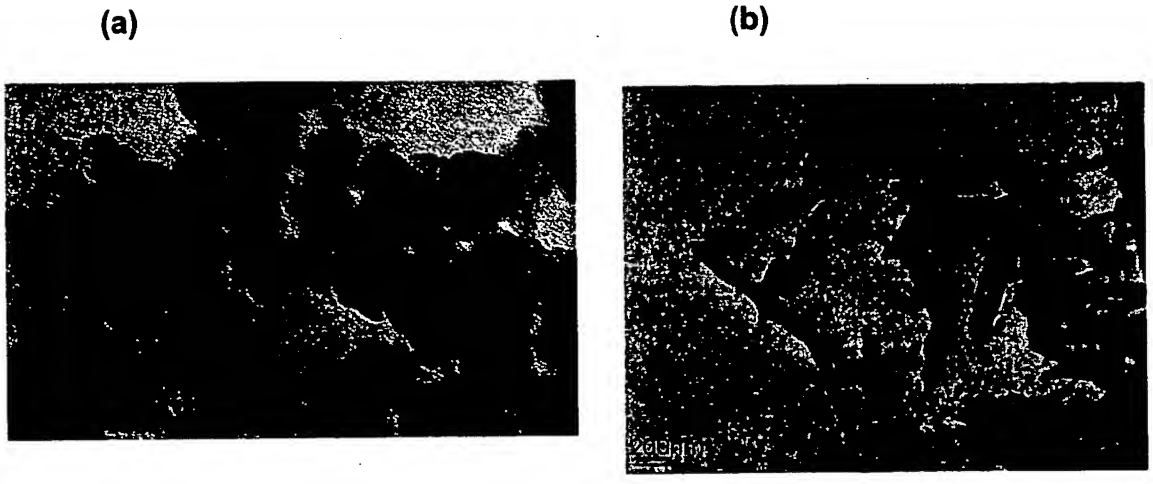

Fig. 2. TEM micrograph of (a) superparamagnetic Fe_3O_4, (b) elongated ferrimagnetic gamma-Fe_2O_3.

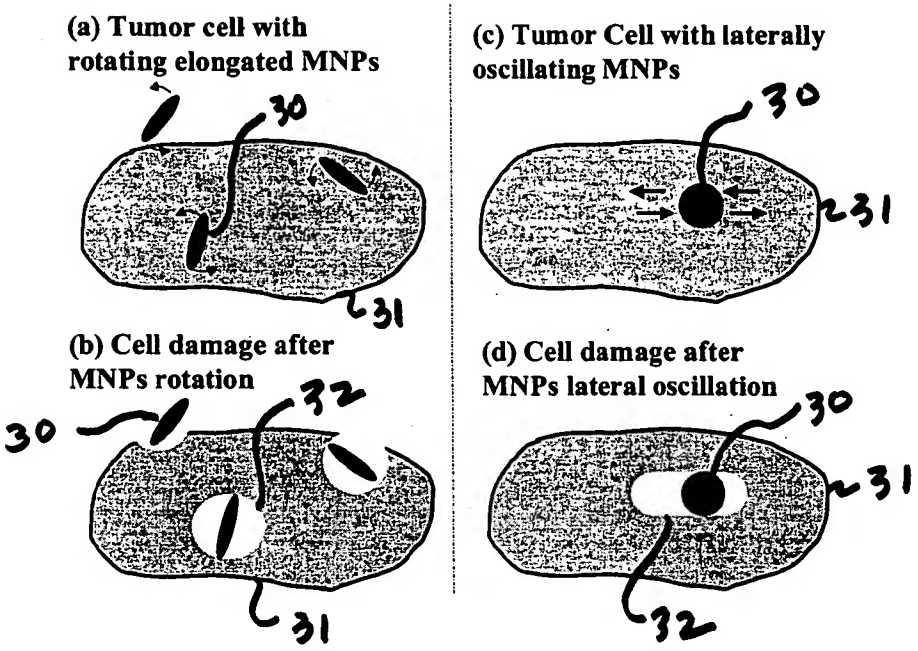

Fig. 3. (a),(b) Tumor cell damage by rotation of elongated magnetic particles, (c),(d) By lateral motion.

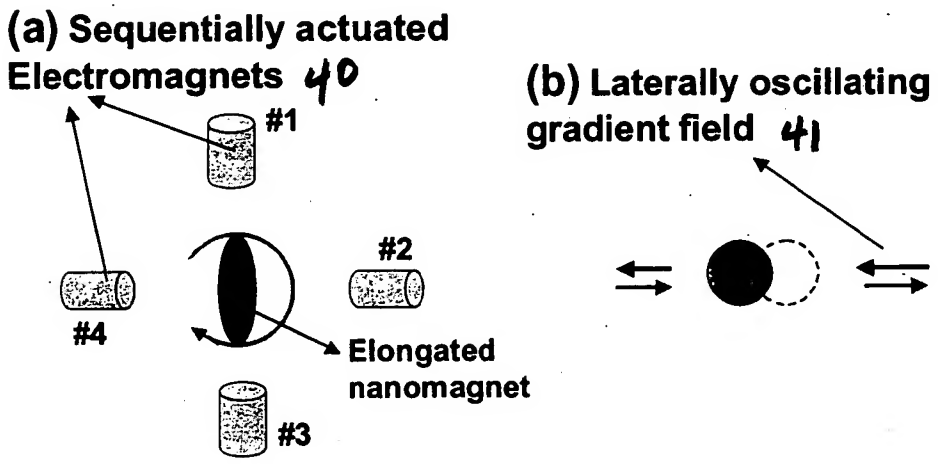

Fig. 4. Apparatus for providing (a) rotational field, and (b) oscillatory lateral magnetic field for particle movement.

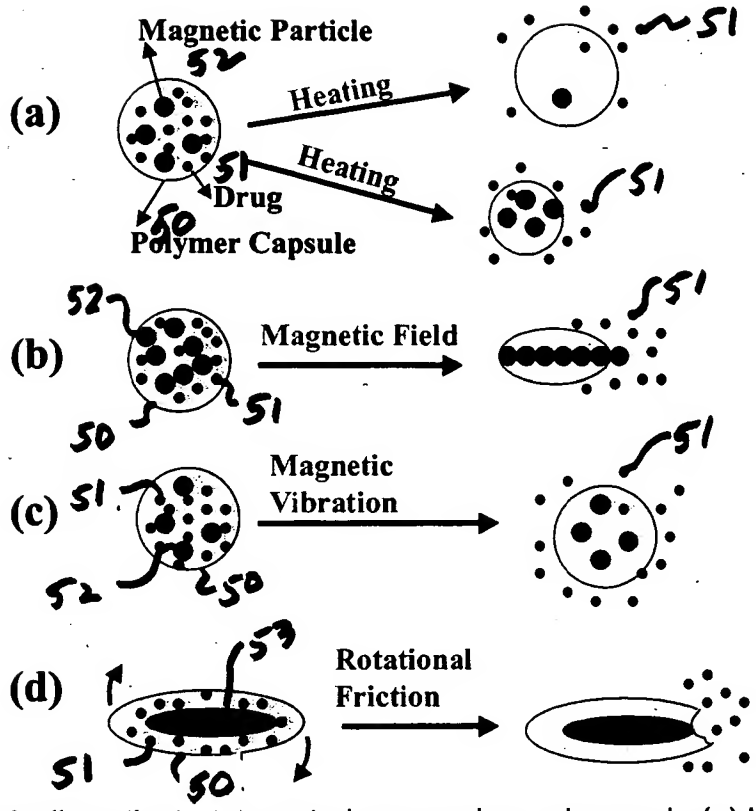

Fig. 5. Magnetically-activated, targeted cancer drug release via (a) hyperthermia heating, (b) applied magnetic field, (c) magnetic-induced vibration, (d) frictional wear.